

REMARKS

Following entry of this amendment, claims 21 to 34, 35, and 40 to 45 are pending in the application. Claims 34, 35, and 40 to 45 are currently under consideration. Claims 38 and 39 have been canceled without prejudice or disclaimer. Applicants expressly reserve the right to pursue the subject matter of those claims in another application.

Double patenting

The Examiner objected to claim 38 as allegedly “being a substantial duplicate of claim 39.” Action at page 2. The Examiner alleged that “[a] transgenic mouse is a mouse whose cellular genome, including somatic cells and germ cells, comprises a transgene or a targeting vector. Therefore, both somatic cells and germ cells will comprise said transgene or targeting vector.” *Id.*

Solely to expedite prosecution and without acquiescing to the objection, applicants have canceled claims 38 and 39 without prejudice or disclaimer. Applicants note, however, that a transgenic mouse can comprise a transgene or a targeting vector in a subset of cells. For example, that situation would be present if the transgenic mouse is a chimeric mouse that has been made, for example, by injecting a blastocyst with embryonic stem cells comprising the transgene or targeting vector. Applicants assert that such a transgenic mouse is encompassed by claim 34.

Applicants assert that the Examiner’s objection to claim 38 is moot in view of the cancellation of that claim.

Written description rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 34, 35, and 38 to 45 as allegedly failing to comply with the written description requirement. Action at page 2. The Examiner provided several bases for the rejection, which will be addressed individually.

First, the Examiner alleged that “[t]he phrase ‘introducing a vector into a collection of mouse embryonic stem (ES) cells’ in amended claim 34 is considered new subject matter.” *Id.* The Examiner contended that “[a] ‘collection of mouse ES cells’ can mean a plurality of different types of mouse ES cells or a plurality of same type mouse ES cells. The specification only discuss introducing the describe vector into any eukaryotic cells that can be genetically manipulated and grown in culture.” *Id.*

Applicants respectfully traverse. Adequate written description requires that an applicant describe the claimed invention in sufficient detail that one skilled in the art would reasonably conclude that the applicant had possession of the claimed invention. MPEP § 2163(I). The Examiner must consider the specification as a whole “from the standpoint of one of skill in the art at the time the application was filed.” MPEP § 2163(II)(A)(2). Finally, “[i]f a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.” MPEP § 2163(II)(A)(3)(a).

As an initial matter, it is not clear what point the Examiner intends to raise when he states “[t]he specification only discuss introducing the describe vector into any eukaryotic cells that can be genetically manipulated and grown in culture.” Action at page 2. It appears that the Examiner is alleging that the specification does not describe

introducing the described vector into eukaryotic cells that *cannot* be genetically manipulated or grown in culture. Applicants note, however, that such embodiments would be inoperative. Applicants assert that there is no reason, and certainly no requirement, for the specification to describe inoperative embodiments. Applicants traverse that basis for the rejection for at least that reason.

Applicants further assert that one skilled in the art, considering the specification as a whole at the time the application was filed, would recognize that applicants had possession of a method comprising “introducing a vector into a collection of mouse embryonic stem (ES) cells,” as recited in claim 34. Applicants previously pointed to page 6, lines 3 to 20, and page 31, lines 17 to 25, of the specification as exemplary support for the amendments to claim 34. Amendment and Response filed January 18, 2007, at page 14. While applicants believe the previously cited passages provide support for the phrase “introducing a vector into a collection of mouse embryonic stem (ES) cells,” additional support for that phrase can be found in the specification, e.g., at page 28, line 25, to page 29, line 1, which states

The presently described libraries may be made by a process comprising the steps of treating (i.e., infecting, transfecting, retrotransposing, or virtually any other method of introducing polynucleotides into a cell) a **population of cells to stably integrate a vector** containing the 3' gene trap cassette, identifying or otherwise selecting for stably transduced cells, and identifying the trapped 3' cellular exons. In a preferred embodiment, the animal cell libraries comprise mammalian cells, and in a particularly preferred embodiment, **the mammalian cells are embryonic stem (ES) cells.**

(Emphasis added.) The specification further states that the ES cells may be mouse ES cells, e.g., at page 31, lines 17 to 20.

Applicants assert that one skilled in the art would recognize that applicants had possession of a method comprising “introducing a vector into a collection of mouse embryonic stem (ES) cells” from at least the cited passages. One skilled in the art would further understand that the recited mouse ES cells encompass those mouse ES cells that “can be manipulated to insert a gene trap vector into the genome of a cell,” as discussed in the specification at page 8, lines 17 to 19. Moreover, applicants assert that one skilled in the art would recognize that applicants had possession of the claimed method using either a collection comprising a plurality of the same type of ES cells or a collection comprising a plurality of different types of ES cells, so long as the mouse ES cells “can be manipulated to insert a gene trap vector into the genome of a cell.” See *id.* Thus, applicants assert that the phrase “introducing a vector into a collection of mouse embryonic stem (ES) cells” is adequately supported by the specification.

Next, the Examiner alleged that the phrase “identifying at least one mouse ES cell comprising the vector” in claim 34 is new matter. Action at page 3. The Examiner stated that the page 6, lines 3 to 20, of the specification “discusses identifying eukaryotic cells having mutated gene(s) using the described vectors.” *Id.* The Examiner then concluded without explanation that the specification does not provide support for the language “identifying at least one mouse ES cell comprising the vector.” *Id.* at pages 3 to 4. According to the MPEP, the Examiner must provide evidence or reasons why a person skilled in the art would not recognize that the specification supports the recited language. See MPEP at § 2163. Because the Examiner failed to

provide such evidence or reasons, applicants assert that the Examiner failed to meet his burden and this basis for the rejection is improper and should be withdrawn.

In the interest of furthering prosecution, however, applicants will address this basis for the rejection. Applicants respectfully traverse. Applicants assert that one skilled in the art, considering the specification as a whole at the time the application was filed, would recognize that applicants had possession of a method comprising "identifying at least one mouse ES cell comprising the vector," as recited in claim 34. Applicants previously pointed to page 6, lines 3 to 20, and page 31, lines 17 to 25, of the specification as exemplary support for the amendments to claim 34. Amendment and Response filed January 18, 2007, at page 14. While applicants believe the previously cited passages provide support for the phrase "identifying at least one mouse ES cell comprising the vector," additional support for that phrase can be found in the specification, e.g., at page 10, lines 16 to 20, which states that "one embodiment of the present invention contemplates vectors that are engineered to incorporate, and optionally express, a marker gene that facilitates the tracking and **identification of target cells that incorporate the presently described 3' gene trap cassette.**" (Emphasis added).

Identification of mouse ES cells comprising vectors is further described in the specification, e.g., at Section 6.2, which discusses the selection of G418-resistant ES cell clones after introduction of a vector that comprises a β geo gene. See, e.g., specification at page 62. One skilled in the art would recognize that selecting G418-resistant ES cells is one way of "identifying at least one mouse ES cell comprising the vector," as recited in claim 34. Thus, applicants assert that the phrase "identifying at

least one mouse ES cell comprising the vector” is adequately described in the specification.

The Examiner also alleged that the phrase “making a transgenic mouse...from at least one identified mouse ES cell that comprises the vector” in claim 34 is new matter. Action at page 3. Again, the Examiner failed to provide any evidence or reason why one skilled in the art would not recognize that the specification supports the recited language, and thus failed to meet his burden. See MPEP § 2163. For at least that reason, applicants assert that this basis for the rejection is improper and should be withdrawn.

In the interest of furthering prosecution, however, applicants will address this basis for the rejection. Applicants respectfully traverse. Applicants assert that one skilled in the art, considering the specification as a whole at the time the application was filed, would recognize that applicants had possession of a method comprising “making a transgenic mouse...from at least one identified mouse ES cell that comprises the vector,” as recited in claim 34. Applicants previously pointed to page 6, lines 3 to 20, and page 31, lines 17 to 25, of the specification as exemplary support for the amendments to claim 34. Amendment and Response filed January 18, 2007, at page 14. While applicants believe the previously cited passages provide support for the phrase “making a transgenic mouse...from at least one identified mouse ES cell that comprises the vector,” additional support for that phrase can be found in the specification, e.g., at page 56, line 34, to page 57, line 2, which states that “[m]ice can subsequently be produced from ES cells containing gene trap mutations in the

genes selected, and the resulting phenotypes can be rapidly identified and characterized.” (Emphasis added). Applicants assert that one skilled in the art, reading the specification, would recognize that applicants had possession of a method comprising “making a transgenic mouse...from at least one identified mouse ES cell that comprises the vector,” as recited in claim 34.

Next, the Examiner alleged that “[t]he phrase ‘an internal ribosome entry site operatively positioned between said promoter and an initiation codon of said exon sequence’ in amended claim 40 is considered new subject matter.” Action at page 4. The Examiner alleged that “[t]here is no description regarding the positional order of a translation initiation codon and the internal ribosome entry site.” *Id.*

Applicants respectfully traverse. Applicants assert that one skilled in the art, considering the specification as a whole at the time the application was filed, would recognize that applicants had possession of a vector comprising “an internal ribosome entry site operatively positioned between said promoter and an initiation codon of said exon sequence,” as recited in claim 40. Applicants previously pointed to page 4, lines 3 to 40, of the specification as exemplary support for the amendment to claim 40. Amendment and Response filed January 18, 2007, at page 14. While applicants believe the previously cited passages provide support for the phrase “an internal ribosome entry site operatively positioned between said promoter and an initiation codon of said exon sequence,” additional support for that phrase can be found in the specification, as discussed below.

Applicants note that “[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.” See MPEP 2163(II)(A)(3)(a). Applicants assert that one skilled in the art would recognize from the specification and the knowledge in the art that applicants had possession of a method comprising introducing a vector into ES cells, wherein the vector comprises “an internal ribosome entry site operatively positioned between said promoter and an initiation codon of said exon sequence.” For example, the specification discusses synthetic exons “useful for the vectors of the invention [including], for example, a high efficiency, or consensus, ribosome binding site or **an IRES sequence 5' to the translation initiation codon of an open reading frame or exon.**” Specification at page 22, lines 29 to 33. Applicants assert that one skilled in the art would further recognize that the IRES sequence is located between the promoter and the initiation codon of the exon sequence. A promoter controls the transcription of the exon into mRNA, and the IRES sequence causes binding of the ribosome to the mRNA in order to translate the exon, starting at the translation initiation codon. Thus, one skilled in the art would recognize that the IRES sequence is located between the promoter and the translation initiation codon; if the IRES sequence were located upstream of the promoter, it would not be present in the mRNA and would therefore be ineffective at causing translation of the mRNA.

Claims 35 and 41 to 45 ultimately depend from claim 34. Thus, for at least the reasons discussed above for claim 34, those claims are also adequately described by the specification. Claim 40 depends from claim 34 and is adequately described by the specification for at least the reasons discussed above for claim 34 and claim 40.

Applicants respectfully request reconsideration and withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph.

Enablement rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 34, 35, and 38 to 45 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Action at page 4. Applicants will address each of the Examiner's bases for the rejection below.

First, the Examiner alleged that "[t]he specification fails to provide adequate guidance and evidence for how to make a somatic transgenic mouse or a germ line transgenic mouse comprising the claimed 3' gene trap cassette by using murine ES cells." Action at page 5.

Applicants assume that this basis for the rejection relates to claims 38 and 39, which recited that the transgenic mouse comprising the vector is a somatic transgenic mouse and a germ line transgenic mouse, respectively. Solely to expedite prosecution and without acquiescing to the rejection, applicants have canceled claims 38 and 39. As discussed above, however, applicants note that a transgenic mouse can comprise a transgene or a targeting vector in a subset of cells. For example, that situation would be present if the transgenic mouse is a chimeric mouse that has been made, for example, by injecting a blastocyst with embryonic stem cells comprising the transgene or targeting vector. Applicants assert that such a transgenic mouse is encompassed by claim 34. Applicants further assert that such a transgenic mouse is enabled by the specification and the knowledge in the art. For example, the specification states that "[s]ince ES cells can be injected back into a blastocyst and incorporated into normal

development and ultimately germ line, the mutated ES cells of the library effectively represent a collection of mutant transgenic mouse lines (see generally, U.S. Patent No. 5,464,764 issued November 7, 1995, herein incorporated by reference).” Specification at page 31, lines 20 to 25. Certain methods of making transgenic mice from ES cells and blastocysts are known in the art and are described, for example, in the cited U.S. Patent No. 5,464,764, and the documents cited therein.

Second, the Examiner alleged that “[t]he specification also fails to provide adequate guidance and evidence for how to use the produced somatic transgenic mouse or a germ line transgenic mouse for the study of basic biological processes and the development of therapeutics and diagnostics for diseases.” Action at page 5. The Examiner further alleged that “[a]bsent a genetic mutation of a gene or a phenotype of the transgenic mouse, one skilled in the art would not know how to use the transgenic mouse produced by the claimed method, for example, to determine the effect of a particular genetic mutation on the efficacy of a drug.” *Id.* at page 6.

Applicants respectfully traverse. The test for enablement is “whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.” MPEP § 2164.01. “Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted.” MPEP § 2164.08; *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). Moreover, “[a] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the

experimentation should proceed.” MPEP 2164.06; *In re Wands*, 858 F.2d 731, 737

(Fed. Cir. 1988).

Claim 34 recites:

34. A method of making a transgenic mouse comprising a vector, comprising:
- a) introducing a vector into a collection of mouse embryonic stem (ES) cells, wherein the vector comprises a 3' gene trap cassette, comprising in operable combination:
 - i) a promoter;
 - ii) an exon sequence located 3' from and expressed by said promoter, said exon sequence not encoding an activity conferring antibiotic resistance; and
 - iii) a splice donor sequence located at the 3' end of said exon sequence;
- wherein the vector does not encode a sequence that mediates the polyadenylation of an mRNA transcript encoded by said exon sequence;
- b) selecting mouse ES cells that comprise the vector integrated into the genome;
 - c) identifying at least one mouse ES cell comprising the vector, wherein the integration of said vector results in the mutation of a gene of the mouse, and wherein the mutated gene has been identified after integration of the vector; and
 - d) making a transgenic mouse comprising the vector from at least one identified— mouse ES cell that comprises the vector.

As an initial matter, applicants note that the claimed method produces a transgenic mouse *wherein the mutated gene has been identified*, that is, a transgenic mouse with an *identified genotype*.

Applicants assert that one skilled in the art would know how to use a transgenic mouse with an identified genotype. For example, such a transgenic mouse can be used to determine the effect of a particular genetic mutation on the efficacy of a drug. As examples of such uses, applicants previously submitted three documents: Hawkins et al, “Inactivation of p53 Enhances Sensitivity to Multiple Chemotherapeutic Agents,” *Cancer Res.* 56: 892-898 (1996); Link et al., “Cardiovascular Regulation in Mice Lacking

α_2 -Adrenergic Receptor Subtypes b and c," *Science*, 273: 803-805 (1996); and Jones et al., "Promotion of mammary cancer development by tamoxifen in a mouse model of Brca-1-mutation-related breast cancer," *Oncogene*, 34: 3554-3562 (2005).

See Amendment and Response filed January 18, 2007. Each of those documents shows the use of a mouse with an identified genotype to determine the effect of a genetic mutation on the efficacy of a drug. Applicants assert that those documents support applicants' assertion that one skilled in the art could use a transgenic mouse having an identified genotype produced by the claimed method.

The Examiner alleged, however, that "[t]he cited references do not use a 3' gene trap cassette to make transgenic mice and they fail to provide evidence for what kind of transgenic mice can be produced by using the claimed method and how to use said produced transgenic mice to determine the effect of a particular genetic mutation on the efficacy of a drug." Action at pages 6 to 7. Applicants assert that it is irrelevant whether the cited documents used a 3' gene trap cassette to create the transgenic mice discussed therein. The present specification and the knowledge in the art adequately enable one skilled in the art to carry out the claimed method of making a transgenic mouse having an identified genotype. The Examiner does not challenge the enablement of making such mice. Rather, the Examiner's contention appears to be that once the transgenic mouse having an identified genotype has been made, one skilled in the art would not know how to *use* that transgenic mouse. Applicants assert that Hawkins, Link, and Jones demonstrate the use of such transgenic mice. Applicants further assert that such uses are not dependent on the particular method by which the transgenic mice were made.

Third, the Examiner alleged that “[i]t appears that certain ‘phenotype’ of the transgenic mouse is required to determine ‘efficacy’ of a particular drug. Absent a phenotype, it is unclear how to determine ‘efficacy’ of a particular drug associated with a particular genotype of a transgenic mouse.” Action at page 8. Finally, the Examiner alleged that “[a]bsent a phenotype, one skilled in the art at the time of the invention would not know how to use the transgenic mouse produced by the claimed method.” *Id.*

Applicants respectfully traverse. As discussed above, applicants assert that one skilled in the art could use the transgenic mouse *having an identified genotype* produced by the claimed method, e.g., to determine the efficacy of a drug in the transgenic mouse as compared to a wild-type mouse. Applicants maintain that an identified phenotype is not required in order to use the transgenic mouse in that manner. While the determination may provide phenotypic information (having a different response than a wild-type mouse to a drug is, in and of itself, a phenotype), such information is generally not known *before* the study is carried out. Rather, one skilled in the art would use a transgenic mouse having an identified genotype to determine if that mouse responds to a drug the same as, or differently from, a wild-type mouse. The result of that determination may provide valuable information. For example, it may provide the mechanism of the drug, the function of the mutated gene, and/or the predicted response to that drug of patients having a particular genotype. Applicants assert that the specification and the knowledge in the art teach one skilled in the art how to use a mouse having an identified genotype in such a manner without undue experimentation.

Applicants respectfully request reconsideration and withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph.

Applicants respectfully assert that the application is in condition for allowance and request issuance of a Notice of Allowance. If the Examiner does not consider the application to be allowable, applicants request that she call the undersigned at (650) 849-6656 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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Dated: August 13, 2007

By: _____



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